STRATEGY FOR FITTING NEURONAL MODELS TO DUAL PATCH DATA UNDER MULTIPLE STIMULATION PROTOCOLS

GongyuY.Shen [1,2] , Shuming Ye[1], Wei R.Chen [2] , Jens Midtgaard [3],
Gordon.M.Shepherd[2], Michael L.Hines[2]
[1]Zhejiang University, School of Life Sciences, Hangzhou, China 310027
[2]Section of Neurobiology, Yale School of Medicine, New Haven, CT 06510
[3]Department of Medical Physiology, Panum Institute, University of Copenhagan
Blegdamsvej, Copenhagan 2200, Denmark
email: shengy@mail.hz.zj.cn

Abstract- **It is a difficult task to fit a neuronal model to data under multiple stimulation protocols. The protocol of weakest stimulation was used first to fit the model at the initial stage. The strategy of fitting an action potential (AP) consisted of three parts: passive parameter fitting, reduction of spatial complexity, reduction of temporal complexity. The nearly linear response of a neuron in the early depolarization well before AP initiation was used to fit the passive parameters with all the ion channel densities set to zero. We separated the fitting of the intervening part between the two electrodes from that beyond the dendritic electrode to reduce the spatial complexity by using dendritic voltage clamp simulation. The decomposition of stimulation protocols and the time course of an AP proved feasible and successful.**

Keywords- Action potential, model, fitting, strategy

I. INTRODUCTION

Neurons have widely diversified complex morphology of dendritic trees. Besides the passive properties of neuronal membrane that comprise specific membrane resistance and capacitance, specific intracellular resistance, neurons are endowed with a repertoire of voltage-dependent ion channels on their cell membranes. So far, many different voltage dependent ion channels have been identified, such as fast sodium, delayed potassium, transient potassium, high-threshold calcium, low threshold calcium, calcium-dependent potassium ion channel. The characteristic behaviors of ion channels are very nonlinear and diverse. Moreover, the density and type distribution of the ion channels on neuronal membranes are also inhomogeneous. Both of our experimental and simulation results reveal the complexity of dendritic signal integration and sites of AP initiation. The simulation gives us some significant insight into the underlying mechanism. However, the equivalent model of electrophysiological behavior of a neuron is an intrinsic nonlinear distributed system with at least several dozens of parameters in real number. Because many different choices of parameter set of a model with an invariant structure and invariant types and distribution of ion channels can produce the same simulated behavior, it is extremely important to constrain the model parameter range by fitting the model behavior to known experimental data as more as possible to avoid equivocal results.

To make the fitting feasible, it is indispensable to carefully design the strategy for fitting the neuronal model to experimental data because of the high dimension of the parameter space that can not be exhaustively explored. It is almost impossible to implement a fully automatic algorithm that can fulfil the fitting task in place of human intelligence based on a cluster of connected work station computer systems. First, the behavior of the model can be dramatically altered due to very small change of one or two parameters. Secondly, the goodness of a fitting in terms of physiological significance can not be judged merely by fitting errors. Some key parts of the target data curves are much more important than others in the context of the fitting of interest. But the errors of those parts only take a small fraction of the total error. Furthermore, there are many local minima with the same amount of fitting errors, but the fitting qualities in terms of physiological significance can be very different. Now, we introduce an effective strategy for the fitting of nonlinear model of neurons.

II. METHODOLOGY

A. Physiology

Our experimental procedure followed those in Chen et al. [2]. 400-micron thick slices were cut from rat olfactory bulbs. Mitral cells and their cell bodies were identified under infrared

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Abstract

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differential interference contrast microscope. During the recording of whole-cell patch clamp, one electrode was placed on a distal site of the primary dendrite, the other on the somatic region. The dendritic electrode was placed as far from the cell body as possible to obtain as long the inter-electrode distance as possible. There were a total of three cells. Two of them were stimulated with current injection and the other with brief synaptic shocks to the olfactory nerve (ON). The current injection and the synaptic stimulation protocols followed our previous published papers [1,2]. Briefly, The four protocols of current injection stimulation included: weak and strong stimulation of current injection at the dendritic electrode, weak and strong stimulation of current injection at the somatic electrode. The intensity of ON shock was controlled at weak, median and strong level which caused weak, median and strong excitatory post-synaptic potential (EPSP).

B. Modeling and Simulation

The morphological structure, kinetic equations and density distribution of voltage-dependent ion channels of the Hodgkin-Huxley models can be found in our previous paper [1]. They were invariant here. Our model under current injection protocols contained a total of 43 parameters that needed to be fit to the dual patch recording data. The intensity and time interval of the stimulating current were known from the experiment. The equations of the glutamatergic EPSP can be found in [5]. EPSP consisted of both α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) components. The time constants for AMPA and NMDA components were obtained from [6]. Besides the 43 parameters, there were two additional unknown parameters that needed to be fit for each EPSP stimulation protocol. All the unknown parameters were fit to the data for each cell with the same strategy stated below. The simulation of the models was carried out with NEURON [3].

III. RESULTS

Each stimulation protocol generated a pair of AP curves. There were four pairs (total eight curves) of APs to which the behavior of the model with just one set of parameters needed to be fit simultaneously. For the cell of EPSP stimulation protocol, the membrane potential of the model with just one set of parameters should be fit to three pairs of data. The stimulation intensities of the current injection were: 0.4nA and 0.8nA for weak and strong somatic stimulation, 0.5nA and 0.8nA for weak and strong dendritic stimulation. However, the EPSP intensities were unknown although the intensities of pre-synaptic shocks to the ON were known.

In order to reduce the computational complexity, an AP was temporally divided into three parts: passive depolarizing charging, onset and upstroke, and the downstroke with the afterpotential. In fact, the main mechanisms of the three parts are markedly different.

The passive charging of the membrane potential is largely caused by the early part of EPSP (or current injection). The region of symmetrical transfer impedance determined this early passive part. The forward transfer impedance was the quotient of the somatic membrane potential divided by the intensity of the injected current at the dendritic electrode. The backward transfer impedance was that of the dendritic potential divided by the intensity of the injected current at the somatic electrode. If the time curves of the forward and backward transfer impedance were superimposed well, this time region was identified as linear charging interval which was shown in Fig.1. In this passive region, only passive electrical and morphological parameters (total seven parameters) were fit.

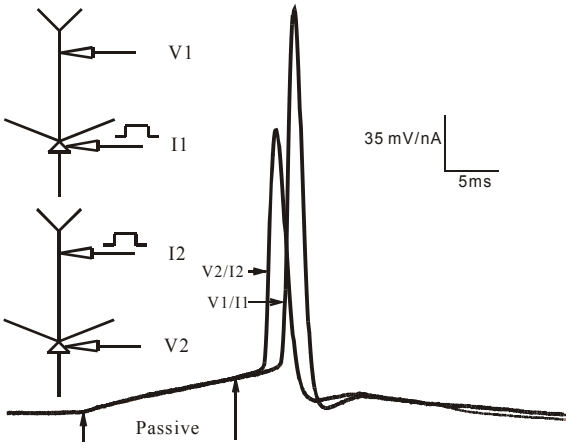

Fig.1. Symmetrical interval of transfer impedance. The neuron's behavior in the symmetrical region was linear.

A critical fitting approach was adopted to separate the fitting of the intervening part between the two electrodes from that beyond the dendritic electrode. The waveforms of experimentally measured dendritic APs were used in place of the simulation curves. Because the simulated dendritic membrane potentials were voltage-clamped to the data, the parameters of the distal primary dendrite beyond the dendritic electrode, tufted dendrites and the synaptic stimulation were masked off and would not interfere with the parameters of the

other part during the somatic AP fitting. Only the parameters of the neuronal part below the dendritic electrode were varied to fit the somatic data. The superposition of two pairs of simulation and data of multiple stimulation protocols was shown in Fig.2. The simulation of dendritic potentials in the

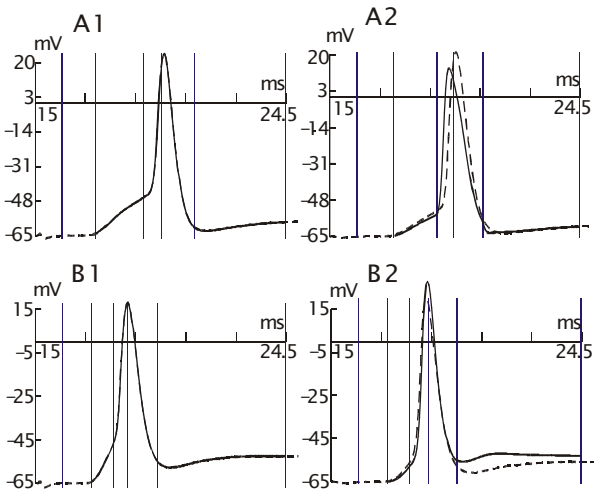

Fig.2 Superposition of data (dashed lines) and simulation (solid lines) which was voltage-clamped. A and B show two stimulation protocols.

left column were voltage-clamped. After the APs at the soma were fitted, the parameters of the fitted part were fixed. Then the voltage-clamp was removed, and the parameters of the part beyond the dendritic electrode and the synaptic stimulation were varied to fit the dendritic data.

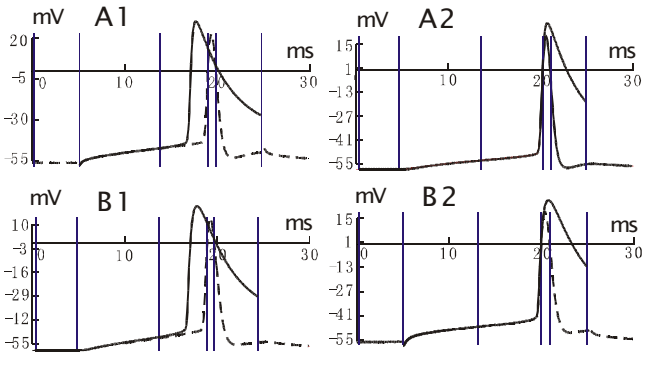

Fig.3 Successive fitting process of the passive part and the onset-upstroke of the APs.

The activation kinetics of the sodium ion channel is mainly responsible for the onset and upstroke of the AP; while he inactivation of sodium ion channel and the activation of the potassium ion channel determine the downstroke and afterpotential. During the fitting of the APs, the passive parameters were fixed and the fitting weights of the passive charging regions were set to large values so that the well-fitted passive charging would not be altered by the active parameter fitting, which was shown in Fig.3. The fitting of the onset and upstroke used only the activation parameters of the sodium ion channel. After the onset and upstroke was well fitted, the parameter values of activation of sodium channel were fixed. Then the inactivation parameters of the sodium ion channel and activation parameters of the potassium ion channel were fit.

As we mentioned earlier, many choices of parameter sets can give a good fitting of simulation of the model to data. Even if the model with a certain set of parameters could produce a quite satisfactory simulation to the data just for one stimulation protocol, it was very likely that the simulation of

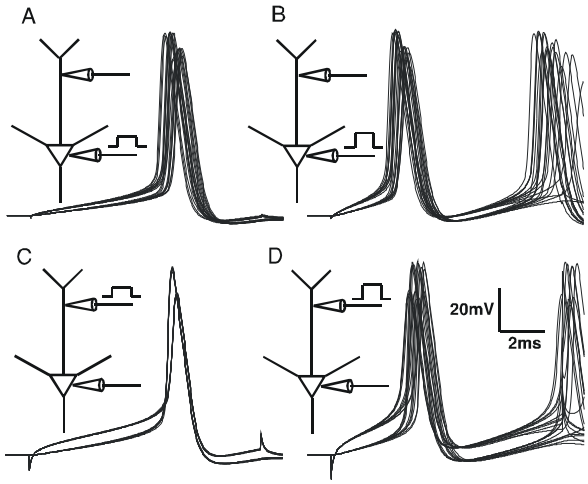

Fig.4. Superpositon of data and simulation of the models constrained with only one stimulation protocol (weak depolarization at the dendrite).

the model could not fit the data under other stimulation protocols as shown in Fig.4 and 5. However, it was very difficult to fit the model with one set of parameters to all the data of four stimulation protocols at the initial stage of fitting. First, only one stimulation protocol was used to fit the dendritic and somatic potential to the corresponding data, which was shown in Fig.4C. The fitted model with different sets of parameters were not well constrained under the other three stimulation protocols and the superposition of many simulation traces was fuzzy around the data curves as shown

in Fig.4A,B and D. After the completion of the fitting for one stimulation protocol, we added a second stimulation protocol in the fitting. With the addition of more stimulation protocols, the model was more constrained and able to produce better simulation under all stimulation protocols. The model constrained with the data of two protocols produced better simulation than with that of only one protocol, which was shown in Fig.5. This strategy of gradual addition of constraints is much more feasible than that of using all the constraints together at the very beginning.

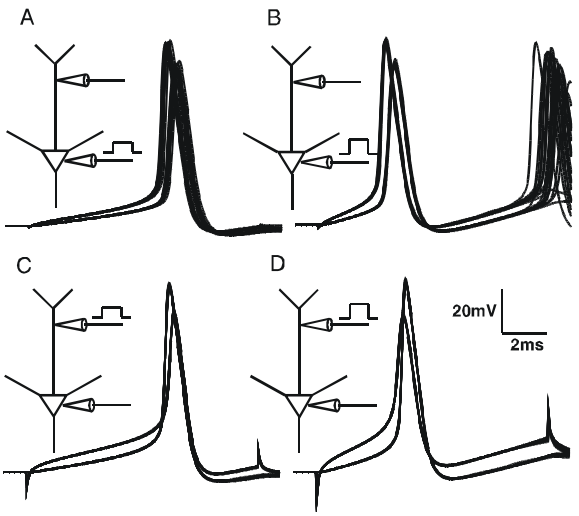

Fig.5. Superpositon of data and simulation of the models constrained with two stimulation protocols (weak and strong depolarization at the dendrite).

IV. DISCUSSION

In fact, the parameters of the model are related with each other. The change of one parameter value will usually affect other parameters' values more or less to maintain the good quality of fitting. Therefore, the fitting of the above approaches must be carried out alternatively for several times until the results of all the fitting approaches converged to an acceptable degree. If the fitting falls into an undesired local minimum, human interference was necessary. The fitting of the early passive charging part has a significant influence on the goodness of the fitting of AP onset, which is the most difficult part to fit. To consolidate the successful fitting results of the previous stages, it is very important to wisely set the fitting weights for different regions of the curves. The evaluation of the quality of a fitting result should be made by both physiologists and neural computational scientists.

V. CONCLUSION

The fitting of a neuronal model to dual patch recording data for multiple stimulation protocols can be decomposed into several less complex approaches. This decomposition can dramatically reduce the computational complexity of the fitting of a non-linear model and make it possible to perform the fitting on an average Unix work station or fast personal computer. With this strategy, we successfully fit three mitral cells perfectly.

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REFERENCES

[1] G.Y.Shen, W.R.Chen, J.Midtgaard, G.M.Shepherd, M.L. Hines, "Computational analysis of AP initiation in mitral cell soma and dendrites based on dual patch recordings," J.Neurophysiol., vol.82, pp.3006-3020, 1999.

[2] W.R.Chen, J.Midtgaard, G.M.Shepherd. "Forward and backward propagation of dendritic impluses and their synaptic control in mitral cells," Science, vol.278, pp. 463-467, 1997.

[3] M.L.Hines, N.T.Carnevale, "The NEURON simulation environment," Neural Computation, Vol.9, pp.1179-1209, 1997

[4] G.Y.Shen, "Model analysis of Graded dendritic spikes in hippocampal CA1 pyramidal cells," ACTA BIOPHYSICA SINICA, 16(3):532-538, 2000

[5] G.Y.Shen, W. R.Chen, J Midtgaard, M L.Hines, G..M.Shepherd, "Role of inhibition of soma and secondary dendrites in initiation of action potential in olfactory mitral cells," Proceedings of IEEE-EMBS Asia-Pacific Conf. on Biomedical Engieering, pp.352-353, September 2000

[6] M.Rapp, Y.Yaron and I. Segev, "Modeling back propagating action potential in weakly excitable dendrites of neocortical pyramidal cells," Proc.Natl.Acad.Sci.USA, 93:11985-11990, 1996